DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-645

Pozen, Inc.
Attention: John Plachetka, Pharm. D.
1414 Raleigh Road
Suite 400
Chapel Hill, NC 27517

Dear Dr. Plachetka:

Please refer to your new drug application (NDA) dated July 31, 2003, received July 31, 2003 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Myzan, formerly MT 100, (naproxen and metoclopramide) tablets.

We acknowledge receipt of your submissions dated the following:

September 23, 2003	February 20, 2004
November 26, 2003	March 2, 2004
January 14, 2004	March 3, 2004
January 27, 2004	March 10, 2004
January 29, 2004	March 12, 2004
February 13, 2004	May 13, 2004

We completed our review and find the information presented is inadequate. Therefore, the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies are summarized as follows:

1. You have not clearly established the efficacy of MT100 in the acute treatment of migraine.

In order for the effectiveness of MT100 to be established as an acute treatment for migraine, you would need to submit at least two adequate and well-controlled trials that demonstrate unambiguous statistically significant superiority of the treatment compared to an appropriate control on a valid measure of pain as well as on the three associated symptoms of nausea, photophobia, and phonophobia. We acknowledge that Study 306 has met these criteria.

However, we have concluded that no other single study you have submitted clearly meets these criteria. In particular, neither Study 308 nor Study 303, when analyzed by the protocol specified analyses, yielded consistently significant drug-placebo differences on all important outcome measures.

We acknowledge that in the factorial studies (Studies 301 and 304), clear statistically significant between-treatment differences between MT100 and a single component on all relevant outcome measures would qualify such a study as one providing evidence of effectiveness. Although this did not

occur in Study 301, in Study 304 almost all of the MT100-metoclopramide comparisons yielded statistically significant differences, save for the proportion of patients experiencing Phonophobia.

However, beside the fact that the between-treatment comparison did not reach statistical significance on the Phonophobia outcome, it is also likely that the between-treatment contrasts on the other major outcomes reached statistical significance because of the extremely large sample size enrolled. That is, the estimate of the treatment effects seen on these outcomes was very small, compared to studies with other approved treatments for migraine (indeed, the estimates of the treatment effects in Study 306 were more consistent with other treatments, and obviously were detected to be significant with far fewer patients than were enrolled in the factorial studies).

2. Even if the effectiveness of the combination had been established in more than one adequate trial, you have not established that both active drug components make a contribution to the claimed effects of the product. Two factorial studies explored the contribution of individual components to the safety and efficacy of the combination: Study MT100-301 and -304. We agree that both studies demonstrate a clear benefit of the combination over metoclopramide for the sustained headache pain relief response, but both studies fail to demonstrate a benefit of the combination over naproxen.

For Study 301, you used a post-hoc "refinement analysis" (ordered logistic regression with baseline pain and investigator site as the covariates) instead of the pre-stated logistic regression analysis. In a March 2000 teleconference, the division notified you that your post-hoc analysis was not acceptable. Using the pre-stated analysis plan, MT100 was not significantly better than naproxen for the primary outcome measure of sustained pain relief ($p=0.077$ according to your analysis; $p=0.064$ according to FDA analysis).

For Study 304, you used ordered logistic regression (with baseline pain and investigator site as covariates) to test MT100 versus naproxen, and MT100 versus metoclopramide. Using that analysis, MT100 was significantly better than both naproxen ($p=0.03$) and metoclopramide ($p<0.001$). However, ordered logistic regression was not the protocol specified primary method of analysis. The protocol specified method was the extended Mantel Haenszel statistic with scores of 0, 1, and 2 for the three ordered categories of sustained pain response, and using a model that controls for center, baseline pain and gender. The division informed you of this discrepancy during the NDA review cycle, and asked you to reanalyze the data according to the pre-stated analysis plan. You performed this analysis using a SAS macro written by Koch. Your reanalysis showed a slightly higher p-value for the comparison of MT100 to naproxen ($p=0.038$ versus $p=0.030$). The division requested that you submit the program and the SAS macro used in your analysis. Using the SAS macro written by Koch, our analysis shows that MT100 was not significantly better than naproxen for the primary outcome measure of sustained pain relief ($p=0.063$). You obtained a different p-value because you apparently mistakenly used equal weight for all strata in your analysis, instead of a weight that is comparable to the stratum's proportion of patients in the trial. To further evaluate the study results, we also analyzed the data by stratifying the center factor only, which is the only factor usually stratified. Our analysis showed a non-significant difference between MT100 and naproxen ($p=0.09$), both with the Koch's SAS macro or with our own SAS program.

In addition to the lack of a statistically significant difference between MT100 and naproxen in the factorial studies, the treatment effect size (for sustained relief) of MT100 over naproxen is clinically marginal (4-6%). As noted earlier, the trend for statistical significance despite the small treatment effect size is probably explained by the very large sample size of the factorial studies (i.e. n=2627 in

Study 304). The lack of benefit of MT100 over naproxen is further supported by the fact that in both factorial studies, MT100 was not statistically different from naproxen for all key 2-hour endpoints (pain, nausea, photophobia and phonophobia) typically used in migraine trials. In addition, MT100 was not statistically different from naproxen for sustained freedom from the key migraine associated symptoms (i.e. sustained nausea-free, sustained photophobia-free, and sustained phonophobia-free).

We acknowledge that the MT100-naproxen comparisons do closely approach statistical significance, and that, therefore, one could argue that, for all intents and purposes, the contribution of the metoclopramide component can be considered to have been demonstrated. In such circumstances, were there an extremely compelling reason to suspend the typical standard for declaring statistical significance, we might be persuaded that these analyses sufficiently document the contribution of metoclopramide. For example, were this product to be shown to provide an important advantage compared to other available products, we might consider its approval.

In this regard, you argue that there are patients who cannot be treated with triptans because of the risk of cardiovascular adverse events, and that this product, therefore, provides a reasonable alternative. It is true that triptans are contraindicated in certain patients, but it is also true that a number of over-the-counter medications (anti-inflammatory drugs) are approved for the treatment of acute migraine, and they are not associated with the cardiovascular risks that are (rarely) associated with triptan use.

Further, chronic use of metoclopramide is known to be associated with a finite risk of tardive dyskinesia (TD), a devastating and often irreversible complication. Although you argue that the intermittent chronic use you would propose in product labeling would not be associated with TD, we do not have evidence that this is true. Indeed, given the number of patients exposed to MT 100 for at least one year in your database (about 300), the absence of any detected cases is consistent with a true rate of TD of about 1%, an unacceptably high risk in the absence of any demonstrated advantage of the product.

In addition, the combination (presumably primarily related to the metoclopramide component) causes multiple malignancies in rats. Although you assert that these malignancies are related to increased prolactin levels in animals produced by metoclopramide, and therefore are irrelevant for humans, you have not adequately documented that the tumor formation is, in fact, the result of increased prolactin levels, other than for the generally accepted case of mammary tumors (although prolactin levels are increased in the animals). Further, and perhaps more important, prolactin levels are increased in humans, and so it is possible that, if increased prolactin is the mechanism of tumor formation in animals, this mechanism might also be applicable to human tumor formation, except, again, for mammary tumors.

Although there is a margin of about 12-28 between levels of metoclopramide demonstrated to be associated with tumors in animals and levels to which humans would be exposed (with no effect level margins of 5-10), we believe that there is at least some evidence that metoclopramide may be genotoxic, thereby at least raising the question of whether such exposure margins are comforting (although we acknowledge that the drug was negative in the p53 mouse study, an assay supposedly sensitive to genotoxic carcinogens).

Taking all of the data together, then, we believe that this product offers no advantage over products currently available for the treatment of acute migraine that would justify altering the accepted standard

for declaring either that the combination has been shown to be effective, or that the metoclopramide component contributes to the overall effect of the combination drug product.

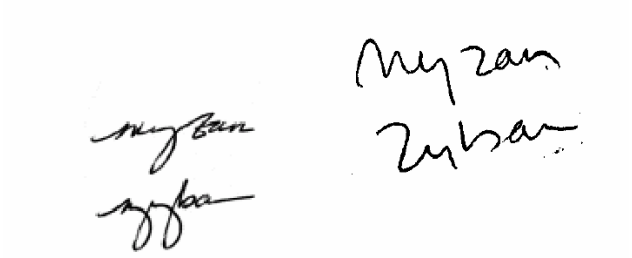
Before we could conclude that substantial evidence of effectiveness of the drug as a treatment for acute migraine has been established, you will need to provide the results of an adequate and well-controlled clinical trial of appropriate size in which the combination is shown to be clearly effective against pain as well as against the three associated symptoms, and which also unambiguously demonstrates the contribution of each component. Further, even if you can establish substantial evidence of effectiveness for this drug as a treatment for acute migraine, you will need to justify the use of this chronically administered product given our concerns about the potential emergence of tardive dyskinesia.

Additionally, the following deficiency, which is not a reason for our not approvable action, has been identified:

Your proposed proprietary name, Myzan, is not acceptable. In reviewing the proprietary name, our primary concerns related to look-alike and sound-alike confusion with Zyban. Zyban (bupropion hydrochloride) is indicated for smoking cessation. The primary visual similarity results from the shared letters of "y" and "an" with identical placement in the names. In addition, both names are comprised of the same number of letters (see below).

Zyban
Myzan

Alternate name recognition and difficulty differentiating names can also be due to the varied styles of scripting the letter "z" (see below).



The similarities in speech may result from the identical second letter of "y" and ending of "an", which is further complicated by the shared two syllable composition. The "z" sound, although in different positions, contributes to sound-alike similarity. In combination, these traits produce a rhyming quality that may result in an alternative auditory and cognitive recognition. The leading letters of "z" and "m" may provide a unique identifier to help distinguish each name, but the rhyming nature of the two names may negate any identification power the leading letters may hold. Verbal orders could easily be confused by transposing the letters.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with this division to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, contact Lana Chen, Regulatory Project Manager, at (301) 594-5529.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Russell Katz

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